REMARKS/ARGUMENTS

Claims 1-5, 7, 8 and 22-29 are pending. Claim 7 is currently amended and new claims 26-29 are presented.

Interview Summary

Applicant thanks Examiner Skowronek for the courtesy of a telephone interview with its representatives, Matthew Zischka and Sally Hemming on May 14, 2007. References of Tullis et al. and Ambrus et al. (U.S. Patent No. 6,528,057) were discussed, although no consensus was reached during the telephone conference.

New Claims

New independent claim 26 and new dependent claims 27 to 29 are presented for the Examiner's consideration. Support for the new claims is found at least at paragraphs [0030] to [0036] of the description. Applicant believes that the new claims add no new matter and are in condition for allowance.

Claim Rejections – 35 U.S.C. §112, 2nd Paragraph

The Examiner rejected claims 7 and 8 as indefinite on the basis that these claims depend directly or indirectly from canceled claim 6. Claim 7 has been amended to depend from claim 4. Applicant respectfully submits that these claims as amended are definite and requests withdrawal of this rejection.

Claim Rejections – 35 U.S.C. §102

In order to sustain a rejection under 35 U.S.C. §102, the Examiner must establish

> "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 1 of the instant application claims a method for detecting the presence of an analyte particle in a fluid.

> The method comprises sequentially:
> (1) filtering a sample of said fluid to remove particles in said sample larger than said analyte particle;
> (2) adding to said sample a reagent that interacts with said analyte particle to form a reagent-analyte particle complex that is larger than said analyte particle;
> (3) filtering said sample to remove particles from said sample that are smaller than said reagent-analyte particle complex;
> (4) testing said sample for the presence of said reagent-analyte particle complex to detect the presence of said analyte particle in said fluid.

As such, the claimed method relies on (1) size filtering an initial fluid to remove particles larger than analyte; (2) a subsequent reagent interaction (by for example an affinity interaction) on the filtered fluid to possibly form a larger reagent-analyte particle complex; (3) and a subsequent further size filtering to remove particles smaller in size than the reagent-analyte complex. The presence of residual reagent-analyte complex in the sample after (3) may then be used to detect the presence of the analyte particle in the original fluid. Conveniently, combining size filtering twice with a reagent reaction such as an affinity reaction allows for easy detection of the analyte in the original fluid, and allows for the construction of a simple testing device. The presence/absence of the reagent-analyte particle in the sample after (3) may be used as an indicator of the analyte in the original fluid.

Section 102(e) Rejection Based on Ambrus et al.

The Examiner has rejected claims 1 to 5 and 22 under 35 U.S.C. §102(e) as being anticipated by Ambrus et al. (US 6,528,057). In particular, the Examiner asserts that Ambrus discloses a method of filtering HIV particles (equated to analyte) from the biological fluid using a filter, that particles larger than the virus are excluded from the filter and that the virus may pass through the filter, separating blood cells from the plasma containing the virus. The Examiner also asserts that Ambrus discloses testing of the sample for the presence of virus-reagent complexes.

The Applicant respectfully disagrees for at least the following reasons.

Ambrus appears to disclose a method for clearing virus from the blood (equated to fluid) of a patient. The device used in the method is designed to allow blood to flow through hollow fibres located in the device, the hollow fibres appear to be formed of a membrane with a pore size that prevents passage of most blood cells through the membrane, but which allows passage of intact viruses and viral particles and fragments (see for example column 4, line 52 to column 5, line 11). Adjacent the hollow fibres (i.e. membrane) are immobilized affinity molecules designed to capture the virus or viral particles (see for example column 4, lines 52 to 59 and column 5, lines 34 to 40). Thus, blood containing the virus is flowed through the device; cells and other components that are larger than the pore size of the membrane pass through the device and do not contact the immobilized affinity molecules. Blood components that are smaller than the pore size pass through the membrane into the areas containing the immobilized affinity molecules. Any components recognized by the affinity molecules (for example, virus, viral particles, viral proteins, etc.) are bound by the affinity molecules, while unrecognized molecules are free to move through the device, including eventually back through the membrane into the core of the hollow fibres and out of the device.

As such, Ambrus does not disclose a method for detecting the presence of an analyte particle in a fluid, as claimed in instant claim 1. Practicing the method of Ambrus simply does not allow detection of the presence of any analyte particle in a fluid. Rather, Ambrus appears to relate to a device for reducing the amount of virus (i.e. analyte) in the blood (i.e. fluid) of an infected patient. The blood is assumed to carry the virus, likely detected by some undisclosed diagnosis of infection.

Ambrus does suggest that viral load can be assessed in the effluent from the device using other known detection methods, including conventional ELISA methods (see column 6, lines 7 to 10). However, the viral load is detected in the effluent, and not on the basis of the presence of the reagent-analyte complex as claimed.

The presence of a viral load in the effluent is not necessarily indicative of the virus (i.e. analyte) in the influent blood (fluid). For example, if the device of Ambrus is fully effective, all detectable virus will be removed from the blood, and the testing of the effluent will not provide any indication of whether the original fluid contains the analyte particle (as is claimed in instant claim 1). That is, fully cleaned blood effluent should test negative, since all existing virus would have been removed and captured within the device described by Ambrus, resulting in a negative ELISA result, which result would be indistinguishable from the result obtained for virus-free blood treated using the Ambrus device.

Ambrus further fails to disclose filtering the sample to remove particles from the sample that are smaller than a reagent-analyte particle complex, as claimed in instant claim 1. Instead, Ambrus merely describes capturing viral particles from the sample that are recognized by the immobilized affinity molecule. Ambrus indicates that the affinity molecules can be directed against, for example, proteins or peptides of the virus. Since the affinity molecules are immobilized, there is no filtration to remove particles that are smaller than a reagent-analyte particle complex (e.g. affinity molecule-virus complex), as

claimed. The pore size of the hollow fibre membrane used in Ambrus is simply not sized with consideration of the reagent-analyte complex. While the device described by Ambrus does describe filtering particles from a blood sample containing a virus (including HIV), the particles that are filtered are not selected based on their size relative to the virus or the affinity molecule-virus complex. Rather, Ambrus suggests that large components such as cells are filtered through the device without contacting the immobilized capture molecules. The membrane of Ambrus preferably has pore sizes 200-500 nm in diameter. Thus, Ambrus discloses filtering the sample to remove particles larger than the pore size of the membrane, which pores are not sized with consideration of the virus size. The result is that if the affinity molecule were not immobilized, the reagent-analyte complex may not be trapped by a membrane pore of 200-500 nm. For example, if the non-immobilized reagent-analyte complex were an antibody-HIV complex, such a complex would likely exit the device along with particles larger and smaller than the antibody-HIV complex.

Thus, any second form of separation that is described by Ambrus is the result of the immobilization of affinity molecules, and does not result from filtering based on the size of any reagent-analyte complex. Applicant submits that there is no disclosure in Ambrus of filtering particles smaller than a formed reagent-analyte complex, as claimed in claim 1.

For all of the above reasons, Applicant submits that Ambrus does not anticipate claim 1. Since claims 2 to 5 depend directly or indirectly from claim 1, Applicant submits that these claims are also not anticipated by Ambrus. Claim 22 specifies that the analyte is HIV, but incorporates the other features of claim 1 and Applicant therefore submits that claim 22 also is not anticipated by Ambrus, for the same reasons.

Applicant therefore respectfully requests withdrawal of the rejection under 35 U.S.C. §102 based on Ambrus.

Section 102(b) Rejection Based on Tullis et al.

The Examiner rejects claims 1 to 5 and 22 as anticipated by Tullis et al. (American Clinical Laboratory, p. 22-23, October/November 2001). The Examiner asserts that Tullis discloses a method of filtering HIV from blood using a filter that separates the cells from the HIV, and discloses the detection of viral-reagent complexes.

Applicant respectfully disagrees for at least the following reasons.

Tullis appears to describe a similar device as described for use in the method set out in Ambrus. Particularly, Tullis describes a standard, hollow-fiber affinity hemodialysis cartridge. The hollow fibers each have multiple submicron-sized pores to allow passage of the virus but prevent preformed blood elements from flowing through the pores. The extra-fiber space includes antiviral antibodies covalently coupled to a solid support.

Tullis describes the pore size of the device only as "submicron". As this term is understood, the pore size is just smaller than 1000 nm. A pore size of just less than 1000 nm would presumably be adequate to achieve the goal set out in Tullis (to prevent preformed blood elements from exiting the fiber; see page 22, the sentence bridging columns 1 and 2), but would be inadequate to filter particles larger than the virus, as claimed in claim 1 (but retain an affinity molecule-virus complex and filter out particles smaller than such a complex).

As well, Tullis does not disclose testing for the presence of reagent-analyte complex (i.e. antibody-virus or antibody-viral protein complexes from the affinity molecule-trapped fraction) in order to detect the presence of the analyte in the original fluid, as claimed in claim 1. In fact, Tullis indicates that in some instances, a patient's viral load in the blood may be below detectable levels (page 23, top of column 1).

At page 23, column 1, paragraph 3, Tullis does indicate that PCR analysis was performed on RNA extracted from virus trapped in the device in order to confirm the effectiveness of the device. However, extraction of RNA followed by PCR amplification will detect RNA and not antibody-virus or antibody-viral protein complexes. Applicant submits that such a disclosure is the use of detection methods already known in the art to detect viral RNA from a given sample, and does not constitute testing of a sample for the presence of a reagent-analyte particle complex to detect the presence of the analyte particle in the original fluid, as claimed in claim 1.

Additionally, Tullis indicates that PCR and p24 ELISA analyses were performed on virus concentrated from plasma. This is direct testing of the sample for the presence of viral RNA or viral protein prior to treatment with the device, and does not constitute testing for the presence of a reagent-analyte complex after filtering to remove particles larger than the analyte and filtering to remove particles smaller than a reagent-analyte complex, as claimed in claim 1.

Therefore, for these reasons, and for the reasons set out in relation to Ambrus, Tullis fails to disclose a method for detecting the presence of an analyte particle in a fluid, or the step of filtering the sample to remove particles from the sample that are smaller than a reagent-analyte particle complex, as claimed in instant claim 1.

Thus, Applicant submits that Tullis does not anticipate claims 1 to 5 and 22 and respectfully requests withdrawal of the rejection under 35 U.S.C. §102 based on Tullis.

Claim Rejections – 35 U.S.C. §103

In order to reject a claim under 35 U.S.C. §103, the Examiner must establish a) that all claim limitations are found in the references and b) motivation in the references or in

the art to modify the references or to combine the references to arrive at the claimed invention; and c) a likelihood of success.

Section 103 Rejection Based on King in View of Coller

The Examiner rejected claims 1 to 5, 7 and 22 to 25 under 35 U.S.C. §103(a) as obvious over King et al. (US 2001/008760), in view of Coller et al.

The Examiner asserts that King describes the use of CD4 coupled to a surface to capture cells expressing the HIV antigen gp120, and that a skilled person will recognize that the method of King is capable of separating viral particles from other particles in a fluid.

The Examiner further asserts that Coller et al. discloses the separation of the Australia antigen from particles smaller than the antigen using a gel filtration column, and separation of the antigen from particles larger than the antigen using cesium chloride gradient centrifugation and labeling of the antigen to aid in its detection. Therefore, the Examiner is of the opinion that it would have been obvious to a skilled person to combine the disclosure of CD4 binding to a surface with the method of Coller to arrive at the instantly claimed method in order to purify the Australian antigen of the Hepatitis C virus.

Applicant respectfully disagrees for at least the following reasons.

Coller does not describe, disclose or suggest filtering the sample to remove particles from the sample that are larger than the Australian antigen (analyte), as described in instant claim 1. Coller does describe use of a cesium chloride density gradient. However, a density gradient does not involve filtration based on size. Rather, a density gradient is a centrifugation method that separates molecules along a continuous gradient based on density. Thus, at most, the cesium chloride density gradient serves to remove the

Australian antigen from particles that are more dense, although not necessarily larger than, the Australian antigen (see column 5, lines 53 to 54, which indicates that the impurities are denser). In fact, Coller indicates (at column 7, lines 23 to 29), that ^{125}I-labeled Australian antigen co-banded on a cesium chloride gradient with unlabeled Australian antigen, which is smaller than the ^{125}I-labeled Australian antigen.

Thus, even if King does describe that a CD4-gp120 interaction can be used to separate HIV from a sample (which is not admitted), King in combination with Coller cannot render the subject matter of claim 1 as obvious, as Coller does not describe, disclose or suggest filtering a sample to remove particles from the sample that are larger than the Australian antigen (analyte), followed by eventual filtration to remove particles smaller than a ^{125}I-labeled Australian antigen (reagent-analyte) complex prior to detection of ^{125}I-labeled Australian antigen to indicate the presence of Australian antigen in the original fluid.

Since claims 2 to 5 and 7 depend directly or indirectly from claim 1, Applicant submits that these claims are also not unpatentable over King in view of Coller. Claim 22 specifies that the analyte is HIV, but incorporates the other features of claim 1, and claims 23 to 25 depend directly or indirectly on claim 22. Applicant therefore submits that claims 22 to 25 are also not unpatentable over King in view of Coller, for the above reasons.

Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103 based on King in view of Coller.

Section 103 Rejection Based on King in View of Coller and Peterson et al.

The Examiner has rejected claim 8 under 35 U.S.C. §103(a) as being obvious in light of King et al. in view of Coller et al. and further in view of Peterson et al. (US

2002/0042125). The Examiner states that Peterson discloses the filtering of virus using a micro-injected molded plastic.

Applicant respectfully disagrees, for at least the following reasons.

Claim 8 depends ultimately from claim 1, and includes the feature of filtering using micro-injected molded plastic.

For the reasons given above, Coller and King in combination do not describe, disclose or suggest a method in which analyte particles are first filtered from particles larger than the analyte particle, followed by eventual filtration to remove particles smaller than a reagent-analyte particle complex. Even if Peterson discloses the use of micro-injected plastic to filter virus particles, as suggested by the Examiner, Peterson does not overcome the deficiencies described above for King in combination with Coller, and therefore further combination with Peterson cannot render the subject matter of claim 8 as obvious.

Applicant therefore respectfully requests withdrawal of the rejection based on 35 U.S.C. §103 based on the combination of King, Coller and Peterson.

Section 103 Rejection Based on Hanna in View of Bernhardt

The Examiner has further rejected claims 1 to 5, 7, 8 and 22 to 25 under 35 U.S.C. §103 as being obvious over Hanna et al. (IEEE Nanobioscience, Vol. 2, No. 1, p. 6-13, March 2003), in view of Bernhardt et al. (US 6,391,657).

Applicant respectfully disagrees for at least the following reasons.

The Examiner asserts Hanna discloses a method of detecting HIV using a system-on-a-chip filter composed of a hollow fiber filter system, and detection of the virus by determining the change in capacitance of a surface coated with the reagent. The Examiner further asserts that Bernhardt discloses the formation of the virus-ligand complexes composed of CD4 receptor-HIV to result in an increased particle size, and that it would have been obvious to a skilled person to combine the method of Hanna with the formation of a complex as disclosed by Bernhardt to arrive at the method of detecting an analyte as claimed in instant claim 1.

However, careful review of Hanna suggests that Hanna describes a system on a chip for capturing and destroying cells infected with a virus such as HIV. The system involves coating a chip with an affinity receptor or ligand that recognizes and captures cells infected with the virus. The chip would be equipped with a mechanism to kill cells, such as a series of electrodes implanted in the surface of the chip that could irreversibly electroporate captured cells. Blood is flowed past the chip, infected cells are bound by the affinity molecules, and attachment is detected by a change of capacitance, activating the cell-lysing mechanism (see page 6, last paragraph to page 7, first paragraph).

Thus, the method of Hanna does not describe a method for detecting an analyte in a fluid that involves two filtering steps based on size in combination with an affinity binding reaction, as specified in instant claim 1. In fact, the method described in Hanna does not involve any size filtering at all. Instead, the method of Hanna relates entirely to affinity capture of target cells by immobilized affinity molecules.

Hanna does very briefly describe a hollow fiber device, referring to a known method of purifying HIV from infected blood. In fact, Hanna appears to describe the device of Tullis (see page 7, last paragraph to page 8, first paragraph) as another approach used to clean infected blood of virus. However, the hollow fiber device is completely independent of the system on a chip, and does not involve detection of bound cells using a

change in capacitance. Hanna does not describe, disclose or suggest combining the hollow fiber device with the system on a chip, or with the use of differential capacitance detection.

In addition, for the reasons set out above in reply to the rejections based on Tullis and Ambrus, even with a brief reference to the device of Tullis, the Hanna reference does not describe, disclose or suggest a method in which analyte particles are first filtered from particles larger than the analyte particle, followed by eventual filtration to remove particles smaller than a reagent-analyte particle complex, and testing of the sample for the presence of the reagent-analyte particle complex to detect the presence of the analyte in the original fluid, as claimed in instant claim 1.

Even if Bernhardt does disclose the formation of the virus-ligand complexes composed of CD4 receptor-HIV to result in an increased particle size (which is not admitted), such a disclosure is not sufficient to overcome the deficiencies of Hanna. Thus, Bernhardt cannot combine with the description of a system on a chip of Hanna to render the present method of claim 1 obvious.

Since claims 2 to 5, 7 and 8 depend directly or indirectly from claim 1, Applicant submits that these claims are also not obvious having regard to Hanna in view of Bernhardt. Claim 22 specifies that the analyte is HIV, but incorporates the other features of claim 1, and claims 23 to 25 depend directly or indirectly on claim 22. Applicant therefore submits that claims 22 to 25 are also not obvious having regard to Hanna in view of Bernhardt, for the above reasons.

Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103 based on Hanna in view of Bernhardt.

Conclusion

In view of the foregoing, it is believed that this application is in condition for allowance. Favourable reconsideration and allowance of this application are requested.

Respectfully submitted,

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